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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/505,377 | 10/20/2004 | Victor V. Lobanenkov | 230295 | 2372 |

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| EXAMINER | |
|---|---|
| GUSSOW, ANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1643 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 04/05/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/505,377 | LOBANENKOV ET AL. | |
| | Examiner | Art Unit | |
| | Anne M. Gussow | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *3-8,10-12,14-22 and 25-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,9,13,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/19/04, 1/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence alignment*.

## DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1, 2, 9, 13, 23 (in part) and 24, in the reply filed on February 14, 2007 is acknowledged. The traversal is on the ground(s) that all of the claims share the special technical feature of a human BORIS polypeptide. This is not found persuasive because a national stage entry (371) application should relate to only one invention, however, combinations of one product, one method of making and one method of using is permissible as explained below from the International Search and Preliminary Examination Guidelines, page 77.

> 10.12 The method for determining unity of invention under Rule 13 is construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application:
>
> (i) in addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product, or
>
> (ii) in addition to an independent claim for a given process, an independent claim for an apparatus or means specifically designed for carrying out the said process, or
>
> (iii) in addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product and an independent claim for an apparatus or means specifically designed for carrying out the said process.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 3-8, 10-12, 14-22, and 25-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no

allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 14, 2007.

3. Claims 1, 2, 9, 13, 23 (in part) and 24 are under examination to the extent that they relate to a nucleic acid.

***Information Disclosure Statement***

4. The information disclosure statements (IDS) submitted on August 19, 2004 and January 19, 2006 have been fully considered and an initialed copy of the IDS is included with this Office Action.

***Specification***

5. The use of the trademarks Marathon™, GeneRacer™, and Bead Beater™ have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The trademark symbols have not been included for the trademarks in this application. Appropriate correction is required for all trademarks throughout.

### *Claim Objections*

6. Claim 23 is objected to because of the following informalities: the claim is drawn in part to the non-elected polypeptide. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 2, 9, 13, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a.) Claims 1, 9, 13, and 23 are vague and indefinite in the recitation of "brother of regulator of imprinted sites (BORIS)" as the sole means of identifying the nucleic acid in claim 1. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. This rejection can be obviated by amending the claims to specifically and uniquely identify BORIS, for example, by SEQ ID NO.

b.) Claim 2 is vague and indefinite in the recitation of "highly stringent conditions". It is not clear what the specific conditions entail.

c.) Claim 23 is vague and indefinite in the recitation of "which method" in the second line of the claim. It is not clear what method is being referred to. This part of the rejection can be obviated by editing the claim to read, "said method".

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 9, 13, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an isolated nucleic acid molecule consisting essentially of a nucleotide sequence encoding human brother of regulator of imprinted sites (BORIS) or a fragment thereof comprising at least 1536 contiguous nucleotides, a vector and cell comprising the nucleic acid and a method of diagnosing cancer by detecting the nucleic acid.

The specification discloses the nucleic acid sequence of SEQ ID No.1 as encoding the polypeptide sequence of SEQ ID No. 2. The specification discloses the human brother of regulator of imprinted sites (BORIS) as SEQ ID No. 2.

The specification does not provide sufficient written description as to the structural features of the claimed genus of fragments comprising at least 1536 contiguous nucleic acids that would encode BORIS. The specification does not disclose BORIS to be a member of a family of well-known proteins. The specification discloses the closest protein to BORIS is CTCF (CCCTC-binding factor), which shares zinc-finger

domains with BORIS but has a distinct function (page 15 paragraph 59). Additionally, Galcheva-Gargova, et al. (Science, 1996. Vol. 272, pages 1797-1802) teach zinc finger protein ZPR1 binds to the cytoplasmic tyrosine kinase domain of the epidermal growth factor receptor (EGFR) suggesting that all zinc finger proteins do not function in binding DNA.

A "representative number of species" means that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]. " See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no

evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.).

It has been well known that minor structural differences even among structurally related compounds can result in substantially different biology, expression and activities. Based on the instant disclosure one of skill in the art would not know which sequences are essential, which sequences are non-essential and what particular sequence lengths identify essential sequences for identifying a BORIS nucleic acid encompassed by the claimed specificity. For example, there is insufficient guidance based on the reliance of disclosure of SEQ ID No. 1 to direct a person of skill in the art to select or to predict particular sequences as essential for identifying BORIS nucleic acids encompassed by the claimed specificities. Mere idea of function is insufficient for written description; isolation and characterization at a minimum are required.

Skolnick et al. (Trends in Biotechnology, 18(1): 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., Abstract and Sequence-based approaches to function prediction, page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular Abstract and Box 2). Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v.

Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Therefore, only SEQ ID No. 1 meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed. (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. Claims 2, 23, and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID No. 2 which encodes brother of regulator of imprinted sites (BORIS), the nucleic acid of SEQ ID No.1, the nucleotide sequence that encodes SEQ ID No. 2 and detecting BORIS in cancer cell lines does not reasonably provide enablement for a nucleic acid that shares 45% or more identity with SEQ ID No. 1 or a method of diagnosing a cancer or predisposition to a cancer. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to an isolated or purified nucleic acid molecule, which (i) encodes the amino acid sequence of SEQ ID No.2 or a fragment thereof comprising at least 307 contiguous amino acids (ii) consists essentially of the nucleotide sequence of SEQ ID No.1 or a fragment thereof comprising at least 1536 contiguous nucleotides, (iii) hybridizes under highly stringent conditions to an isolated or purified nucleic acid molecule consisting essentially of the nucleotide sequence that is complementary to SEQ ID No. 1 or a fragment thereof, or (iv) shares 45% or more identity with SEQ ID No. 1. The claims are also broadly drawn to a method of diagnosing cancer or a predisposition to a cancer in a male mammal, which method comprises detecting either (i) a nucleic acid molecule comprising a nucleotide sequence encoding BORIS or (ii) a polypeptide molecule comprising an amino acid sequence encoding BORIS in a test sample comprising somatic cells obtained from the male

mammal, wherein the detection of (i) or (ii) in the test sample is indicative of the cancer or a predisposition to the cancer in the male mammal, wherein the nucleic acid molecule comprising the nucleotide sequence encoding BORIS comprises SEQ ID No.1.

The specification discloses the nucleotide sequence of SEQ ID No. 1 encoding the polypeptide of SEQ ID No.2 as brother of regulator of imprinted sites (BORIS) (see example 1,. pages 26-27). The specification discloses detection of BORIS mRNA by northern blot in a variety of cancer cell lines (see example 5 and table 1). Applicants have not provided any direction or guidance to assist one skilled in the art in the substitutions, deletions or additions of a nucleotide sequence that would be 45% or more identical with SEQ ID No. 1 and encode the amino acid sequence of SEQ ID No. 2. Further, the as-filed specification fails to address the following issues:

1.) what isolated tumors express BORIS
2.) is BORIS detected in tissue samples from cancer patients
3.) how is a predisposition to BORIS related cancer determined

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess, et al., Journal of Cell Biology, 1990. Vol. 111, pages 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar, et al. Molecular and Cellular Biology, 1988.

Vol. 8 No. 3, pages 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin (Schwartz, et al., Proc Natl Acad Sci, 1987. Vol. 84, pages 6408-6411). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase (Lin, et al. Biochemistry, 1975. Vol 14, pages 1559-1563).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein. Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. The results of the construction of synthetic proteins remain very unpredictable as Burgess, et al., Lazar, et al., Schwartz, et al., and Lin, et al. conclusively demonstrate.

Regarding detection of cancer, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New

York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

There is insufficient evidence that would lead the skilled artisan to predict the ability to detect BORIS in tumors in vivo. The specification does not teach levels of

BORIS mRNA in tumor samples. The specification does not teach the variants of SEQ ID No.1 having 45% or more identity with SEQ ID No. 1 that would encode the amino acid sequence of SEQ ID No.2. Additionally, in the method of detecting cancer, only SEQ ID No. 1 is disclosed as detecting BORIS, not just any DNA encoding BORIS.

In view of the lack of predictability of the art to which the invention pertains and the lack of established protocols for detecting BORIS in tumors, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively detect cancer or a predisposition to cancer by detecting a BORIS polynucleotide which is reasonably predictive that the claimed methods are effective for detecting cancer or a predisposition to cancer, commensurate in scope with the claimed invention.

### *Claim Rejections - 35 USC § 101*

12. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claim 13 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 13, as written, does not sufficiently distinguish over cells as they exist naturally because claim 13 does not particularly point out any non-naturally occurring differences between the claimed cell and naturally occurring cells.

In the absence of the hand of man, the cells are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated" or "purified" cell or similar language would obviate this rejection.

***Conclusion***

14. No claims are allowed.

15. Claims 1, 2, 9, 13, 23, and 24 are free of the prior art. The closest prior art is Hillman, et al. (WO/2002/074913, filed March 14, 2002).

Hillman, et al. teach a human cDNA encoding NAAP22, a nucleic acid-associated protein, that has 40% homology with BORIS DNA and 64.4% homology with BORIS protein of the instant application (see sequence alignment). Hillman, et al. do not teach nor reasonably suggest a nucleic acid that encodes BORIS or detection of BORIS as a diagnosis of cancer or a predisposition to cancer.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571) 272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow, Ph.D.

March 21, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER